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Individualized prediction of transition to psychosis in 1676 individuals at Clinical High Risk: development and validation of a multivariable prediction model based on Individual Patient Data Meta-analysis

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Abstract:

Background: The Clinical High Risk state for Psychosis (CHR-P) has become the cornerstone of modern preventive psychiatry. The next stage of clinical advancements rests on the ability to formulate a more accurate prognostic estimate at the individual subject level. Individual Participant Data Meta-Analyses (IPD-MA) are robust evidence synthesis methods that can also offer powerful approaches to the development and validation of personalized prognostic

models. The aim of the study was to develop and validate an individualized, clinically-based prognostic model for forecasting transition to psychosis from a CHR-P stage.

Methods: A literature search was performed between January 30th 2016 and February 6th, 2016 consulting PubMed, Psychinfo, Picarta, Embase and ISI Web of Science, using search terms ("ultra high risk" OR "clinical high risk" OR "at risk mental state") AND ((conver* OR transition* OR onset OR emerg* OR develop*) AND psychosis) for both longitudinal and intervention CHR-P studies. Clinical knowledge was used to a priori select predictors: age, gender, CHR-P subgroup, the severity of attenuated positive psychotic symptoms, the severity of attenuated negative psychotic symptoms and level of functioning at baseline. The model thus developed was validated with an extended form of internal validation.

Results: Fifteen of the 43 studies identified agreed to share IPD, for a total sample size of 1676. There was a high level of heterogeneity between the CHR-P studies with regard to inclusion criteria, type of assessment instruments, transition criteria, preventive treatment offered. The internally-validated prognostic performance of the model was higher than chance but only moderate (Harrell's C-statistic 0.655, 95% CIs 0.627 - 0.682).

Conclusion: This is the first IPD-MA conducted in the largest samples of CHR-P ever collected to date. An individualized prognostic model based on clinical predictors available in clinical routine was developed and internally validated, reaching only moderate prognostic performance. Although personalized risk prediction is of great value in the clinical practice, future developments are essential, including the refinement of the prognostic model and its external validation. However, because of the current high diagnostic, prognostic and therapeutic heterogeneity of CHR-P studies, IPD-MAs in this population may have an limited intrinsic power to deliver robust prognostic models.

INTRODUCTION

Clinical research on early recognition and intervention of psychotic disorders has enormously expanded over the past two decades (1). There is converging evidence that individuals with an elevated risk for psychosis, commonly termed as at Clinical Risk for Psychosis (CHR-P) (or as 'Ultra High Risk' (UHR) or 'at-risk mental state' (ARMS)), can be identified prior to the onset of a psychotic episode. CHR-P criteria are based by the presence of attenuated psychotic symptoms, brief and intermittent psychotic symptoms with spontaneous remission, or genetic risk for psychosis (2–4), usually combined with functional impairments and help-seeking behaviour (5). CHR-P individuals accumulate several risk factors for psychosis (6) and have a meta-analytical risk of developing psychosis of 20% (95%-confidence interval of 17%-25%) at 2-years (for details see Table 4 in Fusar-Poli et al. (7)) while they are not an increased risk for developing non-psychotic mental disorders (8). The level of risk for psychosis is highest in those with a short-lived psychotic episode, intermediate in those with attenuated positive psychotic symptoms and lowest in those at genetic risk (9). Overall, the meta-analytical prognostic performance of the CHR-P assessment is excellent (AUC of 0.9 at 38-months) (10) and comparable to that of prognostic models used in other branches of somatic medicine. Despite these achievements, to date, the formulation of a prognosis in CHR-P individuals has been limited to group-level predictions. In light of the recent emergence of precision medicine approaches, it is thus important to develop and validate prognostic models that can calculate a personalized risk rather than a group-level global risk estimate. Prognostic modelling combines multiple predictor variables with their relative weight to estimate the risk or probability that an outcome or specific event will occur in an individual patient (11) and is often used in medical sciences such as cardiology or oncology (e.g. (12,13)). The calculated individual risks could then be utilized by the caregiver to inform treatment decisions.

More recently, prognostic models have entered clinical psychiatry (for a methodological review see Fusar-Poli et al (14)). A systematic review has identified seven prognostic models for CHR-P populations, most of which suffer from methodological weaknesses such as the use of suboptimal model building methods, small sample sizes and the lack of internal or external validation (15). Several recommendations for building robust prognostic models in CHR-P populations were made, including the use of large sample sizes, and appropriate events per variable ratios, the selection of a priori predictors on the basis of clinical knowledge or the use of automated selection features through machine-learning methods and the essential need to present validated (internal and external) measures of prognostic performance (14). Some examples of robust prognostic subject-level models for CHR-P populations include the NAPLS risk calculator by Cannon et al (16) (which has been externally validated (17)), the pretest risk enrichment stratification algorithm by Fusar-Poli et al (18) (which has been externally validated), the transdiagnostic risk calculator by Fusar-Poli et al (19) (which has been externally validated twice (20) and implemented in clinical routine (21)) and the functional outcome prognostic model by Koutsouleris et al (22) (internally validated). Yet, the key create-limiting step towards implementation of prognostic models into CHR-P clinical routine is the availability of predictors. Biological and neurophysiological data require more expensive and intrusive assessment methods which are not always available in clinical practice, limiting the clinical utility of these models. Rather, neurobiological-based prognostic models can further refine the prediction of outcomes when used in a stepped sequential framework (23), after simpler prognostic models are applied.

We present here an innovative approach for developing risk prediction models for CHR-P individuals that are based on clinical predictors routinely collected as part of clinical practice. We developed a multivariable (i.e. including several predictors) risk estimation model through

re-analyzing original individual raw data, requested from systemically sought research groups (24), through an Individual Patient Data Meta-analysis (IPD-MA). Prognostic models developed from an IPD-MA offer several unexplored advantages such as large sample sizes, which are of core importance in the case of rare events such as the transition to psychosis from CHR-P stage (25). Moreover, because an IPD-MA leverages the variation in the characteristics of the CHR-P included, it can potentially increase the generalizability of the prognostic model. Furthermore, a prognostic model derived from IPD-MA can statistically take into account the differences in prognostic parameters (such as intercepts and predictor-outcome associations) across the included original studies and can explore under which circumstances the prognostic model predicts optimally (26). Despite these potentials, no IPD-MA has ever been conducted in the CHR-P field.

The primary aim of the current study was to develop and validate an individualized, clinically-based prognostic model for forecasting transition to psychosis from a CHR-P stage using predictors that were selected on the basis of a priori clinical knowledge and that were available in clinical routine.

METHODS

Search strategies

A systematic search strategy was performed to identify relevant original studies. First, an electronic search was performed in PubMed, Psycinfo, Picarta, Embase and ISI Web of Science. The search was conducted between January 30th 2016 and February 6th, 2016. The following search terms were used: ("ultra high risk" OR "clinical high risk" OR "at risk mental state") AND ((conver* OR transition* OR onset OR emerg* OR develop*) AND psychosis). Second, the reference lists of the included articles were manually checked for studies not identified by the computerized search.

Selection criteria

Inclusion criteria were:

- (1) data reported in an original paper in a peer-reviewed journal;
- (2) involved CHR-P subjects 14-40 years old, defined according to established international criteria (1);
- (3) assessed attenuated positive and negative psychotic symptoms as well as level of functioning at baseline using standardized CHR-P measurements;
- (4) reported transition status at follow-up (events);
- (5) reported time to transition or time to last follow-up assessment.

Both longitudinal and intervention studies were included. In the case of studies investigating heterogeneous patient populations, only CHR-P individuals were selected for the analysis. Furthermore, CHR-P individuals who were not meeting the age criterion defined above were excluded from the analysis, as well as CHR-P patients who were already psychotic at baseline as documented in the corresponding articles.

To achieve a high standard of reporting, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines - Individual Patient Data (PRISMA-IPD, (27) as well as the statement Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) (28). The meta-analysis was registered in the PROSPERO database for systematic reviews and meta-analysis (CRD42017071176).

Selection of predictors

For developing and validating a prediction model, it is recommended to select prognostic variables a priori based on earlier research (28) and clinical knowledge (14). In order to develop a model that is readily applicable in clinical practice, the selected predictors were limited to those routinely assessed in CHR-P clinics and involved demographical and clinical predictors. The a priori selected predictors were age, gender, CHR-P subgroup (attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, genetic risk and deterioration syndrome), baseline severity of attenuated positive and negative psychotic symptoms and level of functioning. The a priori clinical rationale for selecting these predictors is given below. The first predictor is age: in general, youth in their late teens and early twenties have the highest risk of developing psychosis (29) Kessler, et al, 2007), and a meta-analysis revealed that older CHR-P individuals had a significant higher risk for developing a psychotic episode (30). Another recent umbrella review found that being aged 15-35 years is a strong factor associated with an increased risk of psychosis (31). The same umbrella review found that gender, the second predictor in our model, has a clear association with an increased risk of psychosis (31). In fact, gender has already been used as predictor in other prognostic models developed for CHR-P populations (19). The third predictor was the severity of attenuated positive psychotic symptoms such as delusions, unusual thought content and suspicion, which are the most studied and established predictors in CHR-P field, and already used by previous prognostic tools in this group (16). Furthermore, a recent meta-analysis of 33 studies, involving a total of 4227 CHR-P individuals, showed different levels of the risk for psychosis onset, where persons with brief and limited intermittent psychotic symptoms had the highest risk of transition, followed by those with attenuated positive psychotic symptoms, and by those with genetic risk and deterioration syndrome who had the lowest risk (9). Therefore, the CHR-P subgroups were included as three independent predictors, recording whether or not the criteria of each distinctive risk group were met. Attenuated negative psychotic symptoms encompass social amotivation (apathy, anhedonia, asociality) and expressive deficits (alogia, diminished emotional expression) (32) and were selected as the seventh predictor. Attenuated negative psychotic symptoms were predictive of a subsequent psychotic disorder in CHR-P individuals (33,34). The last predictor variable was the level of functioning at baseline: a meta-analysis in CHR-P individuals confirmed that functioning is a strong predictor of transition to psychosis (35).

Data collection

Abstracts were screened independently by two reviewers (AM and NB or MP). Each article was assessed individually, and any disagreements resolved by discussion with a third reviewer. Subsequently, all corresponding authors of the eligible studies identified were contacted to request anonymized individual patient data and regarded as non-responders when no reaction was received after two reminder emails.

Data extraction

From each individual patient, the following variables were included: gender, the baseline age of participant, CHR-P group, the severity of attenuated psychotic positive and negative symptoms, level of functioning, transition status at follow-up and duration of the follow-up period. To get a better understanding of possible factors that may have influenced the performance of the prognostic model across the different studies, as well as to detect factors that may have contributed to the study heterogeneity, we also collected for each study additional data. These data related to the inclusion period, inclusion strategies, in and exclusion criteria, the psychometric criteria employed to define transition to psychosis and the type of CHR-P assessment instruments (for a comparative analysis of CHR-P assessment instruments see

Fusar-Poli et al (36)), and the instruments applied to assess symptoms and functioning.

Data storage

All data was anonymized by the researchers of the original studies and therefore not re-identifiable to an individual patient by the current investigators. All cleaned datasets were stored on a secured server in their original formats and converted to a master dataset. Data were inspected on unusual outliers via range check of the all included variables.

Data transformation

Studies vary in the CHR-P instruments assessing the severity of attenuate positive psychotic symptoms, attenuated negative psychotic symptoms, and functioning. Thus, to make it clinically applicable only one measurement was selected in the model as the primary parameter. The selection of the assessment measure was defined a priori on the basis of clinical reasoning.

Missing data

Missing data was imputed according to Multiple Imputations with Chained Equations (MICE) with 50 iterations sets. As recommended by White and Royston (37), the event indicator and Nelson-Aalen estimator of cumulative baseline hazard were included in the imputation model. Also, the study name of the original data was included as a dummy factor to account for potential between-study heterogeneity. Rubin's Rules were applied to combine the data from the imputation sets (38).

Risk of bias assessment in individual studies

The assessment of the methodological quality of each individual included study is an essential element in meta-analyses (27). The majority of the studies in this IPD-MA have a naturalistic observational design (N=12). As such we used the systematic review of Zeng et al (39), which recommends the Newcastle-Ottawa Scale (NOS) (40), a nine-item scale categorized into three dimensions, namely selection, comparability and outcome. Quality assessment of naturalistic and observational studies in meta-analyses is problematic. In fact, the key components of studies to be assessed on the MOOSE's recommendations were whether the outcome of interest was not present at the start of the study, the follow-up period of the study was long enough for the outcome to occur, and an adequate proportion of the subjects participated in the follow-up cohort (41). The minimal follow-up period in this IPD-MA was set at twelve months. Studies received a positive score for adequacy of follow-up cohort when they had a minimum follow-up rate of 50-80% in cohort studies or 80% in RCTs (42).

Primary outcome

The primary outcome is the transition to psychosis (event) from a CHR-P stage. Transition to psychosis was defined according to the criteria of the Comprehensive Assessment of At Risk Mental State (CAARMS) (2), Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms (SIPS/SOPS (3)), Brief Psychiatric Rating Scale (BPRS (43)), Positive And Negative Syndrome Scale (PANSS (44)) or Structured Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (SCID-IV (45)). CHR-P patient outcomes were recorded as transitioned to a psychosis, no transition or lost to follow-up.

Data analyses

Individuals with a complete follow-up assessment were compared to those lost to follow-up with an independent T-test (continuous variables) or Chi-square test (binary variables) for descriptive purposes. Collinearity of predictors was tested with the variance inflation factor

(VIF) and estimated by the formula $1/(1-R^2)$. An outcome of 4 or lower indicates a low indication of collinearity between the predictors (46).

A parametric survival model with a log-normal distribution for event times was computed (Royston, 2001). The evaluation of the model's performance and generalizability was done with an extended form of internal validation, because of the lack of true external validation data. Therefore, an Internal-External Cross Validation technique (IECV) was applied, which maximized the data available for both model development as well as model validation (26). With the IECV, all studies (M) minus one study were used as a derivation set to develop a prediction model, and the remaining set is used for its external validation. This was repeated for each dataset, leading to M scenarios to investigate consistent model performance, which was combined by applying Rubin's Rules (38). All discovered studies were utilized in the development and validation of the model. A t-test calculated the significance of the final beta coefficients of the predictors.

The model performance was estimated by calculating its discrimination and calibration. Discrimination referred to the model's ability to separate CHR-P individuals who transitioned to psychosis versus those who did not transition. For each study, a bar graph with the frequency distribution of predicted survival of the survival groups was presented, for both 12-months as well as 24-months. For both 12- and 24 months, the bar graph showed ten risk groups, which each represented an equal number of individuals. The distribution of the risk groups, which ranged from 0 (no chance of survival, i.e. transition to a psychosis) until 100 (100% chance of survival, so no transition to psychosis) was determined by the observed survival per study. A well-discriminating model shows a high overlap between the predicted survival and the observed survival in the different risk categories (48). Moreover, Harrell's C-statistics with its 95%-confidence intervals (CI) was calculated per study, which referred to the overall probability that the model estimates a higher risk for the CHR-P individual that does develop psychosis compared to a person that does not. Values of C-statistics higher than 0.5 (random prediction) and lower than 0.6 are considered "poor", from 0.6 and 0.7 are considered "moderate", from 0.7 to 0.8 "adequate", from 0.8 to 0.9 "excellent" and above 0.9 "outstanding", up to 1 (perfect prediction). The C-statistics of all individuals studies was plotted in a forest plot, with the 95%-CI indicating a possible statistical difference from random prediction. Furthermore, for each study, the calibration of the model was calculated, which referred to the agreement between the observed and the predicted outcomes (48) and was presented with its 95%-CI for each individual article in a forest plot. The linear predictor is calculated according to the coefficients of the model and included as a covariate in a Cox Model. The slope of the linear predictor is the calibration slope. The calibration plot can be viewed as a measure of fit of the prognostic model in the CHR-P population: when a study's 95%-CI included the value of 1 it indicated a fit, whereas a 95%-CI not containing a score of 1 implied a serious misfit of the model suggesting that adjustments of the model's intercepts should be considered.

CHR-P studies differed with regard to study design, inclusion period, recruitment strategies, inclusion and exclusion criteria, transition criteria, CHR-P assessment instruments and treatments offered. These characteristics were expected to influence the effects of the prognostic model in this IPD-MA. In meta-analyses, heterogeneity is examined with the Q-statistic and I^2 Index (24). However, in studies that develop prediction models based on IPD-MA, the extent of heterogeneity is better quantified by studying the 95% prediction intervals (50).

All statistical analyses were conducted using R, version 4.2.2 (49) and used the following packages: foreign, mice, micemd, Hmsic, VIM, jomo, flexsurv, metamisc, rms, and pec.

RESULTS

Studies and participants

A total of 2176 papers was identified by the literature search and 43 were deemed eligible for the IPD-MA. The corresponding authors of the 43 studies were contacted, of which 15 agreed to participate and shared all necessary individual patient data needed for the model (see Figure 1). Of the remaining authors seven authors replied to work on the same subject, two were not able to share the essential data and nineteen authors did not reply at all. These 28 studies related to a total of 2815 CHR-P individuals (62.7% of CHR-P eligible subjects), of whom 475 transitioned to psychosis (16.9% of the eligible yet not included subjects). There is a selection bias in that the current IPD-MA included 1676 CHR-P individuals, of whom 386 developed psychosis. This corresponded to 37.3% of all the CHR-P eligible participants.

The participating studies were Access, Detection And Psychosocial Treatment (ADAPT) (51), Clinic for Assessment of Youth at Risk (CAYR) (52), Dutch Prediction of Psychosis Study – Amsterdam (DUPS-A) (53), Early Detection and Intervention Evaluation – Netherlands (EDIE-NL) (54), Early Detection and Intervention-United Kingdom (EDIE-UK) (55), Früherkennung von Psychosen (FePsy) (56), Früherkennungs- und Therapiezentrum für psychische Krisen (FETZ) (57), Green Program for Recognition and Prevention of Early Psychosis (GRAPE) (58), Integrative Neuroimaging Studies in Schizophrenia Targeting for Early intervention and Prevention (IN-STEP) (59), Outreach and Support in South London (OASIS) (Fusar-Poli, et al., 2013), Personal Assessment and Crisis Evaluation (PACE) (61), Programme of Recognition and Therapy (PORT) (62), ROME (63), Sendai ARMS and First Episode clinic (SAFE) (64), and Dutch Prediction of Psychosis Study - Utrecht (DUPS-U) (65).

[Figure 1 about here]

Furthermore, for each included study we checked whether CHR-P individuals met the inclusion criteria. CHR-P individuals younger than 14 years were removed from the data set: ADAPT (N=2), CAYR (N=1), DUPS (N=4), EDIE-NL (N=1), PACE (N=1), Rome (N=19), and DUPS-U (N=14), as well as participants of older than 40 years: FePsy (N=10) and IN-STEP (N=1). Subjects with an elevated risk for psychosis but not meeting the established CHR criteria were excluded: FePsy (n=30), FETZ (N=30), INSTEP (N=4), and DUPS-U (N=4). Similarly, subjects who were already psychotic as reported in the corresponding article were filtered out: EDIE-NL (psychotic at inclusion (N=4), history of psychosis (N=1)). Subjects' data was censored to the primary study protocol stated follow-up period: FePsy (N=1) and CAYR (N=4).

Because of these procedures, a final sample of 1676 individuals fulfilled the inclusion criteria and was included in the IPD-MA. Key details of the included studies are summarized in table 1, more comprehensive information on each study is included in Supplement IV.

[Table 1 about here]

An overview of the comparison of study characteristics is presented in table 2. CHR-P studies worldwide participated in the study and the majority of studies took place in Europe (53–57,60,62,63,65). Three studies concerned a Randomized Controlled Trial (RCT) (51,54,55), one study had a mixed design of both RCT and naturalistic observational design (61), while all the others had a naturalistic observational design. The earlier studies started including individuals in 1993 (61), while the later studies started including in 2013 (60). The inclusion period varied between one year (52) until thirteen years (61). The smallest study contained nineteen subjects (63), while the largest study contained over 400 individuals (61). Despite methodological differences, one inclusion criterion was shared by all studies, namely meeting the clinical high risk criteria of at least one of the high risk groups (GRD, APS, or BLIPS). Eleven studies had additional age criteria (52,54,55,58–64), one study included only

participants with a minimum of nine years of education (58) and another study had as additional criterion that individuals should have no history of antipsychotic medication for over 16 weeks (59). There was a greater variety in the applied exclusion criteria, with only the EDIE-UK (55) study that did not exclude subjects in case of a known organic cause for the presentation of prodromal symptoms. Twelve studies excluded individuals with both a current or a lifetime psychotic condition (51,54,58,60–68). Ten studies excluded individuals with lower intellectual capacities (51,52,54,56,57,59,60,62,64,65), five studies excluded individuals in case of substance use or abuse (52,59,60,63,64). Current or a history of antipsychotic medication was an exclusion criterion in six studies. Two studies excluded individuals with insufficient competence of the primary language (54,66). The presence of a pervasive developmental or autism spectrum disorder was an exclusion criterion in two studies (52,59). In one study, a history of electroshock therapy (59), withdrawing their willingness to be followed by the service (60) or suicide risk due to personality disorder (64) was an exclusion criterion. In the final database, the mean follow-up time was of 32.37 months (SD=31.59) and there were 386 transitions to psychosis (events) (23.0%). Therefore the final Event Per Variable ratio was 1:48, which is below the threshold recommended for building robust prognostic models (14).

Eight out of fifteen studies launched special information campaigns, either targeting only potential sources of participant referrals or the general public (51,52,55,60,62,64,66,67). The campaigns differed in their elaborateness: from a website and folders to workshops, letters in newspapers and advertisement on radio and television. All studies included individuals that were referred to them, but a few studies combined this with the option of self-referral (52,62), referral by a close friend or family member (52) or screening in a help seeking population (54). Six studies offered additional treatment such as case management, cognitive behavioural therapy, psychoeducation for the CHR individuals as well as for family, medication, sport and nutrition groups (52,60–62,64,66). Information on specific treatments that were offered was only available for RCTs; most studies did not keep detailed records of offered interventions.

With regard to the assessment of CHR-P, symptoms and functioning, four instruments were applied to determine whether an individual met the CHR criteria, namely PANSS (44), CAARMS (2), the Basel Screening Instrument for Psychosis (BSIP) (4) and the SIPS/SOPS (3). Positive psychotic symptoms were assessed with five different instruments: PANSS (44), CAARMS (2), BPRS (43), SIPS (69), and the Scale of Assessment of Positive Symptoms (SAPS) (70). Negative psychotic symptoms were measured with four scales: PANSS (44), Scale of Assessment of negative symptoms (SANS) (71), CAARMS (2), and the SIPS (3). Functioning was assessed with five scales, namely the Global Assessment of Functioning (GAF) (72), the Modified- Global Assessment of Functioning (m-GAF) (73), the Children Global Assessment Scale (cGAS) (74), the Social and Occupational Functioning Scale (SOFAS) (75), and the Quality of Life Scale (QLS) (76). Transition to psychosis was determined with four different transition criteria: CAARMS (five studies, (52,54,60,61,64), SIPS/SOPS (four studies, (51,59,63,65), PANSS (three studies, (53,55,62), BPRS (two studies, (56,57), and SCID-1 (one study, (58))

[Table 2 about here]

Quality assessment of individual CHR-P studies

All CHR-P studies received the maximum score of 4 for assessing the study quality with the NOS (40): an adequate check that outcome is not present at the start of the study, an adequate duration of the follow-up period, and an adequate proportion of participants in the follow-up assessments (see supplement 1 and 2). The three RCTs additionally received an extra point for blind assessments.

Data cleaning and preparation

Missing data and multiple imputations

78,6% of the original sample had data on all variables. There was missing data with regard to attenuated negative psychotic symptoms (7,2%), functioning (6,6%), attenuated positive psychotic symptoms (4,8%), CHR-P group (4,2%), age (<0,1%) and sex (<0,1%). 3,8% of the individuals were omitted from the analyses because of missing of follow-up data. There were no differences between CHR-P subjects with and without follow-up with regard to age, gender, type of CHR-P subgroup, attenuated negative psychotic symptoms and functioning at baseline. Only the severity of attenuated positive psychotic symptoms at baseline was significantly higher for CHR-P individuals without follow-up ($t=-6.244$, $df=1563$, $p<.001$).

As noted above, the fifteen included CHR-P studies had applied a variety in assessment instruments with regard to attenuated positive psychotic symptoms, attenuated negative psychotic symptoms and functioning (see table 1). All measurements were tested as the core parameters on the basis of the protocol, yet, although other instruments were applied in more individuals, attenuated negative psychotic symptoms-total score SIPS, attenuated positive psychotic symptoms – total score SIPS and GAF were selected because these had the best predictive performance. SIPS/SOPS is a frequently used instrument in the enclosed studies and is one of the golden standard measurements for positive and negative psychotic symptoms in CHR research (77). For functioning, the primary parameter is the frequently applied Global Assessment of Functioning (GAF) (72). However, because the SIPS were only applied by 18.2% and the GAF by 66.3% of the individuals, there was missing data for 81.8 % (attenuated positive and negative psychotic symptoms) and 33.7% (functioning). Multiple imputations were performed with 50 iteration sets. The data from the variables age, gender, GRD, APS, BLIPS, and functioning (GAF) were used to predict the missing SIPS positive and negative psychotic symptoms scores. The imputations diagnostics are presented in Supplement III.

Testing collinearity

An overview of the estimated VIFs is presented in Table 3. Overall, the majority of the predictor variables showed a VIF close to 1, indicating low shared variance with the other variables. However, the three CHR-P subgroups showed a high level of collinearity. To investigate the influence of the collinearity, all three predictors were one-by-one subsequently omitted from the analysis, leading to a drop in VIF scores of below three, yet barely influencing the outcome of the produced model. Given our aim to develop a prognostic model in which all predictors are assessed for their relative contribution to risk, these predictors were retained in further analysis, in line with the methodological recommendations (14).

[Table 3. about here]

Development and validation of the prognostic model

A parametric survival model with a log-normal distribution is fitted for event times (Royston, 2001): transition to psychosis from a CHR-P stage and time to transition. Supplement V displays the discriminative performance of the prognostic model in the individual studies at 12 and 24 months. Figure 2 shows a forest plot with the 95%-CI of the Harrell's C-statistics of the prognostic model per study and the overall C-statistics.

[Figure 2 about here]

The C-statistic of the model was 0.655 with the 95%-CI of 0.627 - 0.682 and (approximate) 95% prediction interval of 0.614-0.695. Inspection of the forest plot showed that the prognostic performance in the larger studies reached an adequate level, with C-statistics of around 0.700

and 95% CI between 0.54 and 0.87 (52,54,56,57,61,62). This is also visible in the boxplots of the individual studies (see supplement V): the proportion of predicted survival per risk group is relatively equal to the observed proportion, meaning that the model can adequately discriminate between CHR-P individuals with a higher versus lower risk of developing psychosis (1-survival). Yet, smaller studies have lower discriminative adequacy: in the forest plot the 95%-CIs of these studies were broad and included 0.5, which indicated that the model did not discriminate better than chance.

The calibration slope of the model in the individual CHR-P studies as well as overall calibration are displayed in Figure 3.

[Figure 3 about here]

The internal-external validation results for the calibration slope gives an overall estimate of 0.886 (95%-CI of 0.745-1.022), which indicated that at 2-year the predicted probabilities, on average, vary too much. Because the 95%-CI includes 1, the overall calibration slope yields as non-significant. Calibration slopes of the individual studies not overlapping with 1 indicate no need for recalibration. Inspection of the forest plot showed that all studies overlapped with 1, which indicated that the prognostic model calibrates sufficiently well, and there are no direct indications that the parameters of the model should be adjusted with shrinkage methods.

Final model

Table 4 presents the final model with its intercepts; all included predictors have a significant contribution to the prediction, as tested with an independent sample T-test. The scale parameter is 2.119.

[table 4 about here]

Prognostic prediction for individual CHR-P patients

With a parametric survival model with a log-normal distribution for event times, a (cumulative) survival probability can be calculated for time t in CHR-P individual subjects, utilizing the linear predictor (5.777) and the earlier reported scale parameter (78).

The following formula that estimates the risk of psychosis (1-survival) for an individual patient derives from the model:

$$\text{Risk of psychosis} = 1 - (7.543 + 0.179 (\text{sex=female}) + -0.049 \times (\text{age}) + .689 \times (\text{Genetic Risk and Deterioration}) + -0.370 \times (\text{Attenuated Psychotic Symptoms=yes}) + -0.738 \times (\text{Brief Limited Intermittent Psychotic Symptoms=yes}) + 0.006 \times (\text{functioning GAF}) + -0.052 \times (\text{total score negative psychotic symptoms SIPS/SOPS}) + -0.102 \times (\text{total score positive psychotic symptoms SIPS/SOPS})).$$

Case study

Considering a 21-years old female that meets the CHR-P criteria of brief intermittent psychotic symptoms, with baseline GAF score of 65, SIPS/SOPS attenuated negative psychotic symptoms total score of 13 and a SIPS/SOPS attenuated positive psychotic symptoms total score of 8, the predicted 2-year survival would be 0.835. This implies that her probability of developing psychosis within the first 2-year is $1 - .835 = .165$, which is of about 16%.

Heterogeneity

The 95%- prediction interval of the C-statistics (0.614-0.695) shows a moderate range, which indicates that there is substantial heterogeneity between the predictions of the model in the different studies. There is a larger amount of heterogeneity detectable with regard to the overall

calibration slope which shows a rather large 95% CI of 0.745-1.022. This is supported by the large variety in operationalization of symptoms in the different assessment instruments as well as variety in outcome criteria.

DISCUSSION

The aim of this study was to develop and validate a prognostic model based on clinical predictors that are available in clinical routine for forecasting the onset of a psychotic episode in CHR-P individuals, using an IPD-MA. The predictors were selected a priori as recommended by state-of-the-art prognosis guidelines. The predictors encompassed two demographical predictors (age, gender) and six clinical predictors collected at baseline (genetic risk and deterioration syndrome CHR-P subgroup, attenuated psychotic symptoms CHR-P subgroup, brief and limited intermittent psychotic symptoms CHR-P subgroup, severity of attenuated positive psychotic symptoms, severity of attenuated negative psychotic symptoms, level of functioning) predictors. The overall model achieved a C-index of .655, indicating a modest subject-level ability to differentiate between CHR-P individuals with a high risk likelihood that develop psychosis from those at lower risk. The overall calibration slope indicated that the model can significantly distinguish CHR-P individuals who convert to a psychosis versus those who do not. Most of the included predictors showed a significant contribution to the model, with the exception of CHR-P group membership (which was characterized by high collinearity). The removal of these variables from the model indicated that the influence of this collinearity on the final model was non-significant and minor in magnitude.

This is the first IPD-MA and the largest clinical prediction modelling study conducted in the CHR-P field. Indeed, one of the main advantages of developing a prognostic model using an IPD-MA is the possibility of reaching large sample sizes, which enables the building of a more robust prediction model. Moreover, the model's generalizability can be strengthened by the inclusion of several large datasets from all over the world. Ensuring appropriate representativeness of CHR-P samples is pivotal to developing robust prognostic models because of the severe sampling biases that affect this population (18,79,80). Our approach was partially successful. On one side we demonstrated that our a priori selected predictors did produce a prognostic model that forecasted the onset of psychosis at the individual-subject level with an accuracy superior to chance (0.655). From a methodological point of view this confirms that preselecting predictors on the basis of previous knowledge and using all of them in the prognostic model is a robust way for developing risk prediction algorithms. On the other side, the level of accuracy was only moderate. This could be due to the fact that our IPD-MA combined CHR-P studies employing different definitions of predictors and outcomes, and that there were some missing data (81). Furthermore, in order to ensure a prognostic model that could easily be applied in clinical practice, we decided to use only one instrument per predictor (e.g. the SIPS and not the CAARMS, PANSS, SAPS, or BPRS, and the GAF and not the SOFAS, mGAF, cGAS, or QLS). This was pre-specified at the PROSPERO protocol level. This decision resulted in missing data which has to be considered as missing not at random (MNAR). The problem was particularly severe because this led to a rather high level of missing data (81.8% for the attenuated positive/negative psychotic symptoms and 33.7% for the level of functioning). Although the missing data were handled with the recommended multiple imputation techniques (82), it did imbalance the final prognostic model. These choices counterweight the moderate prognostic accuracy of our model because they facilitate its theoretical implementability in clinical routine. Scalability of prognostic models is an essential criterion that should be fully considered beyond the level of prognostic accuracy. In fact, even prognostic models that have a suboptimal (but clearly higher than random prediction) level of prognostic performance can be clinically useful if they can enter clinical routine at scale. For example, a prediction model has recently been developed and validated using a patient data and

machine-learning to predict treatment outcome in depression: the overall performance of this model was of a very similar moderate prognostic performance (0.65) (83).

The next stage would be to refine and improve this model. The first option would be to consider using advanced machine-learning approaches. Yet, there is no strong evidence that these methods can deliver more robust and implementable prognostic models compared to a priori defined statistical models. Interestingly, although the prognostic model described above leveraged machine learning methods, its overall prognostic performance was of a similar level than that of our current model (83). A recent systematic review conducted by methodologists showed no performance benefit of machine learning over logistic regression for clinical prediction models (84). This finding was confirmed by a recent empirical study by our group (85). However, it is possible that machine learning methods could demonstrate some clear advantages with the addition of multidimensional predictors encompassing neurobiological, genetic and other modalities (14). The downside of multimodal approaches is that they tend to deliver more complex prognostic models at the expenses of scalable implementability. This IPD-MA study also calls for more homogeneity in the CHR-P assessment instruments or at least more research in the development of converting formulas. This would have allowed minimizing missing and imputed data. For example, a between-assessment scale converter algorithm for symptom rating in schizophrenia has been developed by van Erp et al (86), which enabled both researchers as clinicians to convert the scores of positive and negative psychotic symptoms assessed by the PANSS, SANS, and SAPS. Similarly, an automatic Python package called “convert” has been developed to convert CAARMS into SIPS scores and vice versa (36). The tool is freely available online at <https://bitbucket.org/ioppn/convert>. Unfortunately, we did not have the raw data on the specific CAARMS or SIPS (P1-P5) subscales to use this package, but we only had the overall severity of attenuated positive/negative psychotic symptoms across these two instruments. Beyond the diversity in the assessment instruments, there is another cause of suboptimal prognostic performance for our model, which are the baseline intrinsic differences in study populations. This is supported by the finding that there is substantial diversity in baseline risks and by the finding that our prognostic model had an adequate level of performance (C-statistic 0.7) in the subset of the largest CHR-P studies. These studies are likely to be those with the highest risk enrichment and less affected by sampling biases which are particularly serious in the case of small CHR-P studies. A meta-analysis by Fusar-Poli et al. (87) demonstrated that these sampling biases are mostly due to the way CHR-P individuals are being recruited for undergoing the initial assessment. Specifically, recruiting CHR-P individuals mostly from the community would dilute the risk enrichment (and therefore the transition risk) compared to samples mostly recruited through the secondary mental healthcare system. This was also reflected by the type of outreach campaigns adopted by each CHR-P clinic. In comparison to CHR-P studies that targeted their outreach campaigns to healthcare referrers, CHR-P studies with outreach campaigns that were focused on the general public were associated lower risk of psychosis. There was also a clear relation between the intensity of the campaign (amount of activities) and a diminished transition risk. In our IPD-MA, CHR-P studies differed strongly with regard to information campaigns, as well as sources of referrals, and this factor may have amplified sampling biases and reduced the prognostic performance of our model.

Another factor that could have modulated the prognostic accuracy of our model may have been the preventive treatments offered to the CHR-P individuals. An earlier meta-analysis (88) examined the preventive effects of antipsychotic medication, dietary supplements, integrated psychological treatments and cognitive behavioural therapy on the transition to psychosis and reported an overall risk reduction pooled across all of these categories of 54% at 12 months of 54% and of 37% at 24 months. However, the evidence remains inconclusive while a more recent

network meta-analysis which included about 1,000 more CHR-P individuals found no evidence to favour specific preventive treatments compared to each other for the prevention of psychosis (89).

Limitations

One limitation of the current study is that it did not account for treatment effects. The majority of the included studies have a naturalistic, observational design and as such are an adequate reflection of current clinical practice. Since subject-level data on preventive interventions was only available for RCTs (51,54,55), the effects of these treatments could not be entered into the model, and as such their effects could not be controlled for. However, as indicated above, the actual effectiveness of preventive treatments for CHR-P individuals is questionable. As such it is unlikely that this factor would have impacted our findings substantially. Another limitation is that documented clinical predictors in transition risk could not be used in our model because these were not recorded in a majority of studies. These predictors are for instance childhood adversities, cognitive biases, social cognition, verbal fluency, beliefs of social marginalization, subjective complaints about motor functioning, urbanicity, and poor premorbid social adjustment. The prediction model could be improved if future studies into risk assessment would measure these risk factors systematically. The main limitation of this IPD-MA was that we were only able to collect a minority of the available data. Because of the sampling biases discussed above, this represents a major barrier to generalizability. It is clear that future IPD-MAs in CHR-P populations face the difficult challenge of collecting all (at least 80%) of potential studies identified. The additional limitation is that we had to disregard some data because of the high heterogeneity of the measurements. Future IPD-MA could benefit from the converting strategies across different scales that have been discussed above here.

Clinical implications

Given the above caveats, implementing the current prediction model in clinical practice is not desirable. This does not imply that the model is overall redundant. Future refinement of the model in specific clinical circumstance can be considered. For example, future research can clarify the characteristics of the largest studies in which this model can perform better. An answer to this question is rather complex, since these studies vary greatly with regard to inclusion strategies, with studies accepting self-referrals or referrals by friend or family (52), studies that screened in help seeking populations (54), as well as specialized secondary care (57). The offered treatments varied from none (56) to studies with different treatment options (52,61). Moreover, CAYR (52) shared data of a relatively short follow-up period of only one year and a transition rate of 9.0%, while FETZ (57) monitored their participants for up to six years and reported a transition rate of 44.7%.

Further research directions

One avenue for further research could be to investigate whether the prognostic quality of the current model can be optimized: even though a common reaction is to develop a new prediction model, the recommendation is to iteratively adjust the model by adding new data (90). The main reason for updating the available model is the opportunity for further improving the stability and generalizability of the model by considering additional predictors. Improving the stability of the current model would result in predicted outcomes less influenced by variation in input and enhance reliability. This updating can vary between simple recalibration (adjusting the intercept of the model) or an overall adjustment of the associations of the predictors with the outcome. The most obvious option for improvement could be found in the inclusion of data from research projects identified in the systematic search that have not shared their data so far.

Yet, another possibility is that IPD-MA in CHR-P could never deliver robust prognostic models, because of the inherited heterogeneity of the underlying population, assessment measurements and preventive treatments. Such a hypothesis may suggest that future prognostic research in the CHR-P field should rather focus on conducting new large scale prospective cohort studies that are well characterized phenotypically.

Conclusion

This is the first IPD-MA in CHR-P individuals and the largest clinical prediction study ever conducted in these patients to date. 1676 CHR-P individuals have been used to develop and validate an individualized prognostic model based on clinical variables to forecast transition to psychosis. The model has a moderate to adequate prognostic accuracy, but there are potential options to improve its performance. At the same time, it is important to acknowledge that prognostic models based on IPD-MA may not be particularly effective in the CHR-P field. Harmonization in the CHR-P assessment instruments is a necessary step towards more homogenous databases that can support the development and validation of more robust prognostic models.

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The conception or design of the work was done by AM, NB, PFP and GP. Original study data was collected by JA, MP, DN, LH, APM, AR, ES, SR, FS, SA, SK, KK, BN, PM, SW, AL, AY, MKA, MA, SV, MK, KM, SD, TZ, HI, MG, PFP. AM coordinated the data collection of the IPD-MA. Data analysis was done by TD, whereby interpretation was performed by AM, HB, NB, PFP and GP. The drafting of the article was done by AM, HB, NB, and GP, and critical revisions were made by NB, SJ, TD, PFP and GP. Final approval of the version to be published was given by AM, NB, HB, SJ, TD, AA, JA, MP, DN, LH, APM, AR, ES, FS, SR, SA, SK, KK, BN, PM, AL, SW, AY, MKA, MA, SV, MK, KM, SD, TZ, LW, HI, MG, FPF, GP.

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Contribution to the field

A psychotic disorder emerges mostly in adolescence and early adulthood and affects up to 4 in 100 individuals. The Clinical High Risk state for Psychosis (CHR-P) has become the cornerstone of modern preventive psychiatry. More recently, individualized prognostic models

have been used to predict a transition to psychosis, but are typically not easily applicable in clinical practice, because required information to make a prediction requires specific equipment or training and is expensive.

In this study, we aimed to build a model to predict who will develop a psychosis based on information that is routinely collected in the clinical field. For the first time, data from CHR-P cohort studies worldwide were used to build this model. In this study we show that our model can moderately predict whether an individual develops psychosis. Despite our positive results, it is also important to acknowledge some relevant limitations. Because of the large variety between the CHR-P studies prediction models based on IPD-Mas in this population may not be able to reach higher performance measures. Harmonization of CHR-P assessments and therapeutic interventions may be the first step to facilitate future IPD-MAs in this field.

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1028 Disclaimer:

1029 None

Table 1. Overview of studies utilized for the development and validation of the prognostic prediction model

Study	Country	Inclusion period	CHR	Positive psychotic symptoms	Negative psychotic symptoms	Functioning	Transition criteria	N (% m)	Age (M, SD)	Follow-up (months)	Transition status at last follow-up (n, %)
ADAPT	Can	2008-2010	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	GAF	SIPS/SOPS	49 (73.4%)	21,3 (3,9)	24	3 (6.1%)
CAYR*	Can	2005-2014	CAARMS	BPRS	SANS	GAF	CAARMS	176 (55.7%)	19,3 (4,0)	12	16 (9.0%)
DUPS-A	NLD	2002-2006	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	GAF	PANSS	69 (66.7%)	20,0 (3,7)	36	18 (26.1%)
EDIE-NL	NLD	2008-2012	CAARMS	CAARMS	CAARMS	SOFAS	CAARMS	195 (49.2%)	22,7 (5,4)	18	32 (16.4%)
EDIE-UK	UK	1999-2002	PANSS	PANSS	PANSS	GAF	PANSS	58 (68.9%)	22,2 (4,5)	36	13 (22.4%)
FePSY*	CH	2000-2015	BSIP	BPRS	SANS	GAF	BPRS	133 (31.8%)	24,2 (5,2)	12 - 78	38 (28.8%)
FETZ	D	1998-2003	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	SOFAS	BPRS	161 (63.3%)	25,3 (6,1)	12 - 72	72 (44.7%)
GRAPE	KOR	2007-2011	SIPS/SOPS	SAPS	SANS	QLS	SCID-I	60 (58.3%)	19,7 (3,3)	20,7	14 (23.3%)
INSTEP*	JPN	2008-2013	SIPS/SOPS	PANSS	PANSS	GAF	SIPS/SOPS	53 (56.6%)	24,0 (8,4)	36	6 (11.3%)
OASIS*	UK	2013-2016	CAARMS	CAARMS	CAARMS	GAF	CAARMS	51 (58.8%)	22,8 (5,2)	17,7	16 (31.4%)
PACE	AUS	1993-2006	CAARMS	BPRS	SANS	GAF	CAARMS	415 (48.2%)	19,4 (3,4)	12-168	114 (27.7%)
PORT*	POL	2010-2016	CAARMS	CAARMS	CAARMS	SOFAS	PANSS	107 (45.8%)	18,8 (3,5)	12 - 84	20 (18.7%)
Rome*	ITA	2012-2013	SIPS/SOPS	PANSS	PANSS	cGAS	SIPS/SOPS	19 (52.6%)	15,3 (1,3)	12-24	5 (26.3%)

SAFE	JPN	2004-2012	CAARMS	PANSS	PANSS	GAF	CAARMS	106 (62.3%)	20,0 (4,4)	28.8	14 (13.2%)
DUPS-U	NLD	2003-2006	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	mGAF	SIPS/SOPS	25 (40.0%)	16,6 (1,6)	60	7 (28%)

Abbreviations: AUS: Australia, BPRS: Brief Psychotic Rating Scale, BSIP: Basel Screening Instrument for Psychosis, CAARMS: Comprehensive Assessment of At Risk Mental State, CAN: Canada, cGAS: children Global Assessment Scale, CH: Switzerland, DSM-IV: Diagnostical and Statistical Manual of mental disorders version IV, GAF: Global Assessment of Functioning scale, ITA: Italy, JPN: Japan, KOR: South Korea, m: male, M: mean, mGAF: modified Global Assessment of Functioning scale, N: NLD: the Netherlands, PANSS: Positive and Negative Syndrome Scale, POL: Poland, QLS: Quality of Life Scale, SANS: Scale for the Assessment of Negative Symptoms, SD: standard deviation, SIPS/SOPS: Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms, CHR: Ultra High Risk, UK: United Kingdom.

*Data from the specified study, yet not identical to the data in the published paper, for instance a subsample of the study or sample with a shortened or prolonged follow-up then reported in the original paper.

Table 2. Summary of study characteristics

	N (studies)	% of studies	% of total sample
Continent:			
Europe	9	60.0	48.8
Australia	1	6.7	24.8
Northern America	2	13.3	13.4
Asia	3	20.0	13.1
Design:			
Naturalistic observational	11	73.3	82.0
RCT	3	20.0	18.1
Mixed	1	6.7	24.8
Start inclusion period:			
Before 2000	3	20.0	37.9
2000-2005	4	26.7	11.9
2005-2010	5	33.3	31.9
2010-	3	20.0	10.6
Inclusion period – duration:			
1 year	1	6.7	10.5
1-2 years	5	33.3	22.3
2-3 years	4	26.7	17.1
>3 years	5	33.3	48.6
Information campaigns			
Yes	8	53.3	50.0
No	7	46.7	50.0
Inclusion strategies			
Referral	12	80.0	71.4
Mixed	3	20.0	28.6
Inclusion criteria: in additional to CHR-group:			
Age at inclusion	10	66.7	74.1
A minimum of nine years of education	1	6.7	3.6
No history of antipsychotic medication for over 16 weeks	1	6.7	3.2
Exclusion criteria:			
Organic cause for prodromal symptoms	14	93.3	96.7
Current or lifetime psychosis	12	80.0	82.9
Intellectual Functioning	11	73.3	67.1
Substance use	5	33.3	24.2
Current or history of antipsychotic medication	6	40.0	53.8
Language requirements	2	13.3	19.5
Diagnosed with pervasive developmental disorder or autism spectrum	2	13.3	13.7
A history of electroshock therapy	1	6.7	3.0
Not help seeking individuals	1	6.7	3.0
Suicide risk due to personality disorder	1	6.7	6.3
Assessment of Ultra high risk:			
SIPS/SOPS	7	46.7	26.1
CAARMS	6	40.0	63.1
PANSS	1	6.7	3.5

BSIP	1	6.7	7.9
Assessment of positive psychotic symptoms:			
BPRS	3	20.0	43.2
CAARMS	3	20.0	21.1
SIPS/SOPS	5	33.3	21.1
PANSS	3	20.0	13.9
SAPS	1	6.7	3.6
Assessment of negative psychotic symptoms:			
SANS	4	26.7	46.8
PANSS	4	26.7	13.6
SIPS/SOPS	4	26.7	18.2
CAARMS	3	30.0	21.1
Assessment of functioning:			
GAF	9	60.0	66.3
SOFAS	3	20.0	27.7
mGAF	1	6.7	1.5
cGAS	1	6.7	1.0
QLS	1	6.7	3.6
Transition criteria:			
CAARMS	5	46.7	56.3
SIPS/SOPS	4	26.7	8.7
PANSS	3	13.3	14.0
BPRS	2	13.3	17.5
SCID-I	1	6.7	3.6
Sample size:			
<50	3	20.0	5.6
50-100	5	33.3	17.4
100-150	3	20.0	20.6
150-200	3	20.0	31.8
>200	1	6.7	24.7
Transition rate:			
<10%	2	13.3	13.4
10-20%	4	26.6	27.6
20-30%	7	26.7	46.5
30-40%	1	6.7	3.0
>40%	1	6.7	9.6
Treatment:			
CBT (RCT)	3	20.0	18.1
Additional treatment	6	40.0	59.0
None	6	40.0	23.1

Abbreviations: BPRS: Brief Psychotic Rating Scale, BSIP: Basel Screening Instrument for Psychosis, CAARMS: Comprehensive Assessment of At Risk Mental State, CBT: Cognitive Behavioral Therapy, cGAS: children Global Assessment Scale, CHR: Clinical High Risk, GAF: Global Assessment of Functioning scale, mGAF: modified Global Assessment of Functioning scale, PANSS: Positive and Negative Syndrome Scale, QLS: Quality of Life Scale, RCT: Randomized Controlled Trial, SANS: Scale for the Assessment of Negative Symptoms, SCID-I: Structured Clinical Interview for DSM-IV, SIPS/SOPS: Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms

Table 3. Predictor variables and accompanying VIF

	Dependent								
		Gender	Age	GRD	APS	BLIPS	Pos Sx	Neg Sx	Functioning
Independent	Gender	-	1.029	1.028	1.028	1.028	1.028	1.005	1.028
	Age	1.021	-	1.022	1.022	1.020	1.012	1.016	1.022
	GRD	7.857	7.875	-	1.026	1.599	7.877	7.877	7.877
	APS	15.127	15.157	1.975	-	1.790	15.122	15.162	15.142
	BLIPS	9.848	9.848	2.004	1.165	-	9.851	9.870	9.855
	Pos Sx	1.415	1.404	1.419	1.415	1.416	-	1.208	1.418
	Neg Sx	1.833	1.867	1.879	1.879	1.879	1.599	-	1.339
	Functioning	1.586	1.589	1.590	1.588	1.587	1.589	1.133	-

Abbreviations: APS: Attenuated Psychotic Symptoms, BLIPS: Brief Limited Psychotic Symptoms, GRD: Genetic Risk and Deterioration, Sx: Symptoms

Table 4. Variables and intercepts of the final model

Variable	Intercept:	T	SE of Mean	Sign.	95%- confidence interval	
					Lower	Upper
Intercept	7,543328648	51.792	.14565	<.001	7.251	7.836
Sex=female	0.179071582	13.247	.01352	<.001	0.152	0.206
Age	-0.048979637	-42.162	.00116	<.001	-0.051	-0.047
APS=yes	-0.369616434	-7.737	.04777	<.001	-0.466	-0.274
BLIPS=yes	-0.738429338	-15.950	.04630	<.001	-0.831	-0.645
Functioning: GAF score	0.006634737	4.059	.00163	<.001	0.003	0.010
Negative psychotic symptoms: SIPS/SOPS-total score	-0.054490819	-14.542	.00375	<.001	-0.062	-0.047
Positive psychotic symptoms: SIPS/SOPS-total score	-0.092850985	-16.356	.00574	<.001	-0.105	-0.082

Abbreviations: APS: Attenuated Psychotic Symptoms, BLIPS: Brief Limited Psychotic Symptoms, GRD: Genetic Risk and Deterioration, SE: Standard Error, Sign.: significance level, SIPS/SOPS: Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms